

**QUARTERLY FOCUS ISSUE: HEART RHYTHM DISORDERS****Viewpoint**

# Implantable Cardioverter-Defibrillator Therapy After Acute Myocardial Infarction

## The Results Are Not Shocking

Jeffrey J. Goldberger, MD, Rod Passman, MD, MSCE

*Chicago, Illinois*

The risk of sudden death is highest early after myocardial infarction (MI) and progressively declines over the ensuing 6 to 12 months. Nevertheless, several randomized clinical trials have failed to show a survival benefit for implantable cardioverter-defibrillators when implanted early after MI in high-risk patients. The etiology of this acute MI–sudden cardiac death paradox is unclear, but may be related to the changing nature of the substrate over the several month period after acute MI. Further investigation is needed to delineate the actual causes of death in the early post-MI period and which interventions can be implemented to reduce the increased rate of sudden death that is observed. (J Am Coll Cardiol 2009;54:2001–5) © 2009 by the American College of Cardiology Foundation

It has been clearly shown in multiple experimental models and in clinical practice that myocardial infarction (MI) may establish the substrate for fatal ventricular tachyarrhythmias both acutely and in the long term. It has also been recognized that these arrhythmias may occur either as primary events, namely, “reversible” arrhythmias, or as secondary phenomenon related to actual or impending mechanical failure. With the advent of the coronary care unit, the immediate identification and defibrillation of these early reversible ventricular tachyarrhythmias has resulted in important improvements in survival. However, it has long been appreciated, and recently confirmed, that the high-risk period for sudden death for patients who survive an acute MI extends beyond the hospitalization period (1,2). Thus, using implantable cardioverter-defibrillators (ICDs) in high-risk patients early after MI has seemed logical and important. Yet, studies evaluating whether the ICD can improve survival after acute MI have failed to show a benefit for this therapy (3). The acute MI–sudden cardiac death paradox thus mandates a re-examination of some of our basic assumptions and a reframing of our approach to better understand the pathophysiology of sudden cardiac death at this time.

From the Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois. Dr. Goldberger receives research support from Medtronic, Boston Scientific, and St. Jude Medical. Dr. Passman receives research support and serves as a consultant for Medtronic, receives research support from GE Healthcare, and is on the Speakers' Bureau for GlaxoSmithKline.

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### Risk of Sudden Cardiac Death After Acute MI

The risk of sudden death after acute MI has been well delineated (1). After the index event, typical survival curves demonstrate a sharp decline initially that plateaus between 6 and 12 months, with variable risk inversely proportional to left ventricular systolic function. For example, in the VALIANT (Valsartan in Acute Myocardial Infarction) study of 14,609 patients with acute MI and either left ventricular dysfunction or congestive heart failure randomly assigned to angiotensin receptor blocker or an angiotensin-converting enzyme inhibitor, or both, the risk of sudden death was highest in the first month after MI at 1.4% per month and declined over 2 years to 0.14% per month. Figure 1 displays the rate of sudden death or resuscitated cardiac arrest in the VALIANT study stratified by ejection fraction. In all ejection fraction groups, the incidence of sudden death was highest early after MI and then rapidly declines.

### ICD Therapy After Acute MI

The preceding data, as well as the documented survival benefit of the ICD in patients with coronary artery disease and left ventricular dysfunction (4–7), provide a convincing rationale to consider the implementation of ICD therapy early after acute MI in high-risk patients. It is interesting to note that many of these trials did not enroll patients within the first 30 days after an acute MI, and the mean time from the acute MI to enrollment, when documented, was often substantially longer (5–7). DINAMIT (Defibrillators in Acute Myocardial Infarction Trial) evaluated early (within 6 to 40 days of acute MI) ICD placement versus medical therapy in “high-risk” post-MI patients with left ventricular

Abbreviations  
and Acronyms

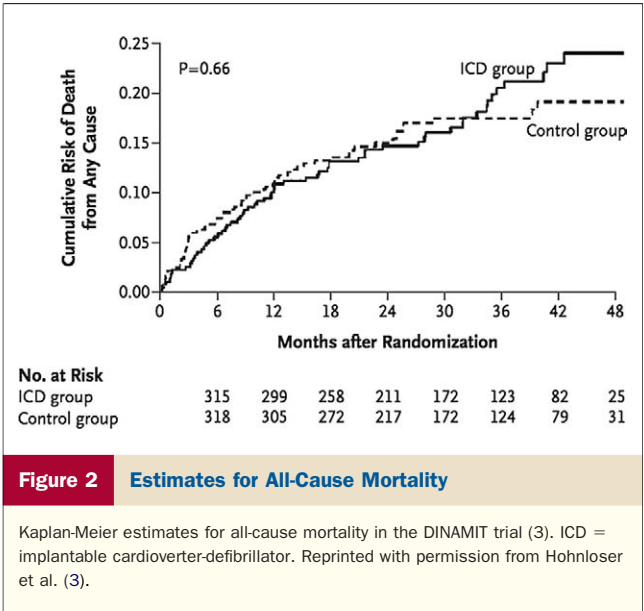
ICD = implantable  
cardioverter-defibrillator

MI = myocardial infarction

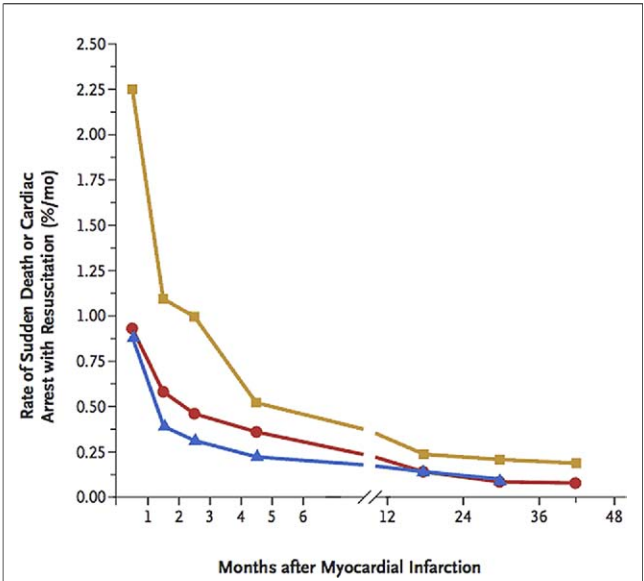
dysfunction (left ventricular ejection fraction  $\leq 35\%$ ) and abnormalities in autonomic tone as measured by heart rate or heart rate variability. There was no difference in overall mortality (Fig. 2) despite a high incidence of arrhythmic events in both groups (3). With an average follow-up of 30 months, the annual mortality rate was 7.5% in the ICD group and 6.9% in the medical therapy group ( $p = 0.66$ ). Data from the IRIS (Immediate Risk Stratification Improves Survival) study (8) were recently presented at the 2009 annual sessions of the American College of Cardiology. In this study, in which patients were enrolled over a period of 8 years, early (within 5 to 31 days of acute MI) ICD placement was compared with medical therapy in “high-risk” post-MI patients with left ventricular dysfunction (left ventricular ejection fraction  $\leq 40\%$ ) and resting heart rate  $\geq 90$  beats/min, or nonsustained ventricular tachycardia at  $\geq 150$  beats/min. Over a 3-year follow-up period, there was no difference in mortality (22.9% vs. 22.0%,  $p = 0.76$ ). These clinical trials have surprised many clinicians and have prompted efforts to explain the failure of these trials to demonstrate a benefit of ICD therapy in this setting.

**Explaining the Acute MI–Sudden Cardiac Death Paradox**

As the risk of sudden death is highest immediately after acute MI and declines over time, it is a paradox that ICDs



reduce mortality only when implanted well after the index event despite their near uniform success in successful defibrillation of life-threatening ventricular arrhythmias. Assuming that the data are correct, there appear to be at least 3 plausible explanations. First, sudden cardiac death is not synonymous with an arrhythmic event. It is therefore possible that the increased incidence of sudden death that is noted after acute MI is largely not due to reversible lethal ventricular arrhythmias. If so, an ICD would not be expected to have an impact on this type of sudden death. Alternatively, the risk predictors that have been used to identify the high-risk population postulated to be susceptible to reversible lethal ventricular arrhythmias may actually select for nonarrhythmic causes of death in the early post-MI period. It is possible that different risk stratifiers are necessary to identify patients who will experience reversible ventricular tachyarrhythmias that might benefit from an ICD. Lastly, the act of device implantation and testing may in some way be deleterious so that whatever potential benefits ICDs may provide are offset by these negative effects. Whether the actual causes of sudden death differ in the early post-MI period or whether the risk predictors for identifying patients susceptible to reversible ventricular tachyarrhythmias differ in the early post-MI period, the dynamic changes in substrate that occur post-MI may account for these time-dependent changes.



**Figure 1**     **Rates of Sudden Death or Cardiac Arrest**

Rates of sudden death or cardiac arrest with resuscitation after acute myocardial infarction, stratified by left ventricular ejection fraction (LVEF). The **yellow line** indicates LVEF  $\leq 30\%$  ( $n = 3,852$ ); the **red line** indicates LVEF 31% to 40% ( $n = 4,998$ ); and the **blue line** indicates LVEF  $>40\%$  ( $n = 2,406$ ). Reprinted with permission from Solomon et al. (2).

**Anatomic, Ionic, and Neuronal Remodeling**

To understand why the pathophysiology of sudden cardiac death early post-MI may differ from the pathophysiology of sudden cardiac death later post-MI, it is necessary to consider the spectrum of remodeling changes that may occur after an acute MI. An understanding of the interplay between remodeling and risk for arrhythmias is essential to

the development of any future insights designed to prevent fatal arrhythmic events in this population.

Alterations in cardiac structure and function induced by MI are responsible for the observed elevations in both acute and long-term risks of sudden death after the index event. Cardiac remodeling can be defined clinically in relation to the changes in ventricular size, shape, and function that occur after myocardial injury, pressure, or volume overload. These clinical changes are determined at the tissue level through altered genome expression and molecular, cellular, and interstitial changes regulated principally by hemodynamic load and neurohormonal activation.

At the cellular level, myocardial pathologic changes accompany left ventricular remodeling and involve myocyte hypertrophy and fibroblast hyperplasia accompanied by an increase in collagen deposition within the interstitium. Within hours of infarction, extracellular matrix is digested and results in wall thinning and infarct expansion. In the weeks after an MI, nonuniform anisotropy results from increases in connective tissue, collagen, and edema between cells in the epicardial border zone (9). Neurohormonal agents, local growth-promoting peptides, and physical factors later result in cardiac hypertrophy. In those persons in whom these compensatory mechanisms fail to maintain cardiac output, ventricular dilation begins and heralds the onset of symptomatic heart failure and its associated hazards (10).

In conjunction with the anatomic changes induced by MI, alterations in ion channels of both infarcted and noninfarcted tissue cause changes in excitability and repolarization that promote re-entry. Peak inward calcium currents are reduced in myocytes isolated from the infarcted border zone regions, and recovery of the fast inward sodium current may also be delayed (11). In areas remote from the infarct, cellular hypertrophy can result in prolongation of action potential duration and marked heterogeneity in repolarization times due to reductions in the transient outward potassium current (12).

On a neuronal level, sympathetic nerve fibers distributed in perivascular areas and between myocytes of the infarcted region may become injured during infarction, and the distal stumps undergo Wallerian degeneration (13). Afterward, re-expression of neurotrophic factor genes from around the site of injury may trigger regeneration in the axonal sprouts proximal to the site of injury, possibly in an attempt to re-establish neuronal control of contractile function (14).

Although the exact mechanism of neuronal remodeling is unknown, Zhou et al. (15) have demonstrated that infarcted myocardial cells locally release nerve growth factor and growth-associated protein (GAP43), resulting in a cascade of increased regionalized expression of neurotrophic substances and their retrograde transport to the left stellate ganglion. The effects at the ganglionic level trigger more extensive growth of cardiac sympathetic neurons (15,16). When nerve sprouting forms synapses with other fibers, regional increases in sympathetic hyperinnervation results.

The exact mechanisms by which denervated regions predispose to arrhythmogenesis is unclear. However, denervation supersensitivity has been proposed as a possible explanation whereby myocardial tissue deprived of sympathetic innervation responds to sympathetic nerve stimulation or norepinephrine infusion with an exaggerated shortening of the effective refractory period (17,18). This effect may be exaggerated in ischemic or infarcted tissue and lead to the development of ventricular tachyarrhythmias. Whether these arrhythmias are as effectively treated by the ICD as those due solely to fixed anatomic substrates or other etiologies has not been established.

Clinically, the time-dependent changes in ventricular remodeling may occur over a period of years. Gaudron et al. (19) evaluated time-dependent changes in ventricular remodeling in patients after acute MI. Over a period of up to 7 years, there was progressive left ventricular dilation that was particularly striking among those who died. Further efforts to understand both the time course of all remodeling changes that occur after MI and the factors that determine which patients are destined to have the most adverse remodeling are warranted so that preventive therapies can be targeted to these patients.

### **Could Early Post-MI Sudden Death Not Be Due to Reversible Ventricular Tachyarrhythmias?**

In this postulated scenario, there may be 2 periods of risk for sudden cardiac death with different underlying pathophysiology: an early period in which ICD therapy is ineffective, and a later period in which ICD therapy is effective. The early period would be characterized by the ongoing changes described above, and the later period would be characterized by a fixed substrate resulting from the remodeling. An important study supporting this notion is a retrospective analysis of MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) (20). In this report, there was no benefit to ICD implantation when used for primary prevention of sudden death in post-MI patients with reduced ejection fractions when the ICD was implanted within 18 months of the MI. However, there was substantial benefit to the ICD when implanted >18 months after the MI. Both the DINAMIT and IRIS studies also support this concept as there was no ICD benefit even when the patients were followed up to 30 to 36 months. These data support the notion that there may be an extended period of time on the order of at least 1 to 2 years after MI in which an ICD may not improve survival, at least under the current implant indications.

Further support for a different pathophysiology for sudden death in the early post-MI period derives from the EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) investigators (21). They demonstrated that eplerenone, a selective aldosterone blocker with numerous properties including inhibition of ventricular remodeling and collagen deposition,



decreased the overall risk of sudden cardiac death by 21% when given to patients with acute MI complicated by left ventricular dysfunction and heart failure (21). Further analysis of the data reported a 37% reduction in sudden cardiac death within 30 days of randomization for enrollees with an ejection fraction  $\leq 40\%$  and a 58% reduction if the ejection fraction was  $\leq 30\%$  (22). In sum, these findings support the concept that in the early post-MI period, treatments aimed at affecting remodeling impact sudden death whereas treatments focused solely on treating the arrhythmias once they occur appear ineffective.

### **Are Different Risk Predictors Needed in the Early Post-MI Period to Identify Patients Who Will Experience Reversible Ventricular Tachyarrhythmias?**

An alternative explanation for the lack of ICD benefit observed early after an MI is that the selection criteria for identifying patients at risk for treatable ventricular tachyarrhythmias may need to be different in the early post-MI period in which active remodeling is ongoing. There are no data that firmly support this contention. However, the BEST+ICD (Beta-Blocker Strategy Plus ICD) trial (23) provides some interesting insights. This trial was terminated prematurely because of poor enrollment. Patients within 5 to 30 days of an acute MI with an ejection fraction  $\leq 35\%$  and either  $\geq 10$  premature ventricular complexes per hour, depressed heart rate variability, or a positive signal-averaged electrocardiogram were randomly allocated to standard medical therapy ( $n = 59$ ) or to an electrophysiology study-guided ICD strategy ( $n = 79$ ). Only patients with inducible ventricular tachycardia received an ICD. Although the trial was negative, the reported 1- and 2-year mortality rates in the standard medical therapy group were 18% and 29.5% versus 11% ( $p < 0.3$ ) and 20% ( $p < 0.2$ ) for the electrophysiology study guided ICD strategy group. However, these differences were not statistically significant, and the study was too small to make firm conclusions. Despite this limitation, it is interesting to note that the use of a risk-stratification tool that should be fairly specific for ventricular tachyarrhythmias, namely, electrophysiologic testing, was associated with some difference, albeit not statistically significant, in outcome.

In the REFINE (Risk Estimation Following Infarction, Non-invasive Evaluation) study, Exner et al. (24) employed a combined assessment of autonomic tone plus cardiac electrical substrate in an attempt to identify both a high-risk population after acute MI and the optimal timing of risk evaluation. While impaired heart rate turbulence plus abnormal T-wave alternans measured at 10 to 14 weeks after MI best identified patients at high risk for cardiac death or cardiac arrest, no single variable or combination of variables was useful at predicting future cardiac events when measured at 2 to 4 weeks post-infarction. In sum, these studies provide further evidence that the electrophysiologic milieu changes with time after an acute MI and that both the

assessment of risk and the treatments exhibit a degree of time-dependency previously unappreciated.

### **Can ICD Implantation/Testing Early Post-MI Be Associated With Deleterious Effects?**

Several recent studies have suggested that clinical ICD shocks, whether appropriate or inappropriate, may be associated with poor subsequent survival (25-27). While there are many potential explanations for this finding, it is certainly feasible that some patients may be susceptible to deleterious effects of a high-voltage shock. High-voltage shocks have been associated with electroporation manifest by local repolarization changes (28), transient myocardial dysfunction (29), and potential for troponin release/elevation (30). Whether these potentially deleterious effects of an ICD shock occur with greater frequency in the setting of a healing versus healed MI has not been studied. This potential interaction between shocks and time from MI merits further investigation.

### **Conclusions**

The acute MI-sudden cardiac death paradox has now been firmly established. Given the demonstrated efficacy of ICDs in terminating ventricular tachyarrhythmias, it seems most compelling that sudden cardiac death early post-MI may not be due to arrhythmia alone. However, it is possible that unique risk predictors are needed to identify those patients at risk for primary arrhythmic death post-MI. Finally, a potential deleterious effect of ICD implantation and testing during this period also deserves further exploration.

Once these issues have been clarified, it may be possible to reassess which therapies and which risk predictors should be studied in the dynamic milieu of the early post-MI substrate. Better understanding of these changes and how risk changes over time both quantitatively and qualitatively is a challenging endeavor that is necessary if the goal is to further reduce mortality during this high-risk period.

**Reprint requests and correspondence:** Dr. Jeffrey J. Goldberger, Northwestern University Feinberg School of Medicine, 251 East Huron Street, Feinberg 8-503, Chicago, Illinois 60611. E-mail: [j-goldberger@northwestern.edu](mailto:j-goldberger@northwestern.edu).

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**Key Words:** myocardial infarction ■ sudden death ■ implantable defibrillator.